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Geertsema, E.M.; Meetsma, A.; Feringa, B.L.

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Asymmetric Synthesis of Overcrowded Alkenes by Transfer of Axial Single Bond Chirality to Axial Double Bond Chirality**

Edzard M. Geerتمa, Auke Meetsma, and Ben L. Feringa*


[1] This work was supported by the Dutch Foundation for Scientific Research (NWO).

[2] Prof. Dr. B. L. Feringa, Dr. E. M. Geertsema, Dr. A. Meetsma Department of Organic and Molecular Inorganic Chemistry University of Groningen Nijenborgh 4, NL-9747 AG Groningen (The Netherlands)

Fax: (+31) 50-363-4296 Email: feringa@chem.rug.nl

[**] This work was supported by the Dutch Foundation for Scientific Research (NWO).
crowded alkenes is still a challenging goal.\textsuperscript{[9]} Methodology has been developed for the synthesis of optically active biaryls in which control of the chirality of an axial single bond is achieved by the coupling of two aryl moieties to a chiral bridge.\textsuperscript{[4]} Based on a related principle we present the synthesis of stable enantiomers of an overcrowded alkene, which features axial double bond chirality, by using \((-\)\text{-}2,3\text{-}O\text{-}isopropylidene-L\text{-}threitol\text{-}1,4\text{-}ditosylate \((S,S)\text{-}1\), \((+\text{-})\text{-}(R)\text{-}1,1'\text{-}binaphthol \((R)\text{-}2\), and \((-\)\text{-}(S)\text{-}1,1'\text{-}binaphthol \((S)\text{-}2\) as chiral auxiliaries. In our most successful approach two halves of the envisioned alkene were first coupled to the chiral bridge. A diastereoselective intramolecular coupling reaction then afforded the corresponding overcrowded alkenes. As no racemization was observed after removal of the chiral bridge this sequence implies the realization of the intriguing concept of conveying axial single bond chirality to stable axial double bond chirality. Moreover, we report for the first time the determination of the absolute configuration of enantiomerically pure thioxanthylidenes as accomplished by X-ray analysis.

Initially we focussed on chiral template \(1\), which is derived from tartaric acid (Scheme 1). An earlier attempt by Yip et al. to prepare optically active bifluorenylidene\textsuperscript{[7]} along these lines resulted in the complete loss of optical activity as a result of the product having a low barrier to racemization.

The preorganized system \((S,S)\text{-}4\) was prepared from 7-methoxy-9-oxo-9H-thioxanthene-2-carboxylic acid \((3)\text{[9]}\) and \((S,S)\text{-}1\). An intramolecular copper-promoted gem-dichloride coupling reaction\textsuperscript{[9]} afforded the sterically overcrowded alkenes \((S,S,M)\text{-}5\) (major product) and \((S,S,P)\text{-}5\) (minor product) in 20\% yield.\textsuperscript{[10]} This rather low yield is a result of the extensive formation of oligomers during the coupling reaction, which unfortunately could not be suppressed by working at high dilution. The newly formed alkene moiety is chiral as a consequence of its folded structure, which explains the formation of two diastereoisomers. A diastereomeric excess of 60\% was determined by \(\text{\textsuperscript{1}H}\) NMR spectroscopy. Recrystallization from acetone gave crystals of pure \((S,S,P)\text{-}5\) that were suitable for X-ray analysis (Figure 1). The unique folded structure of the overcrowded alkene part of \((S,S,P)\text{-}5\) is clearly visible and based on the 2,3,5-configuration of the l-threitol moiety a \((P)\text{-}\text{configuration for the diester moiety is established. The helical structure of (S,S,P)-5 is quantified by torsion angles of 30.6 (C8-C30-C28-C29) and \(-3.9^\circ\) (C9-C8-C30-C28). The major isomer \((S,S,M)\text{-}5\) could not be obtained diastereomically pure, despite several attempts.

In order to develop a synthetically useful asymmetric route we employed \((R)\text{-}2\) and \((S)\text{-}2\) as chiral templates (Scheme 2 for \((R)\text{-}2\), the same procedure was applied for \((S)\text{-}2\). The diester \((R)\text{-}6\) was prepared from thioxanthone \(3\) and \((R)\text{-}2\) in two steps in nearly quantitative yield. More importantly the yield of the subsequent intramolecular gem-dichloride coupling reaction with Cu-bronze increased considerably and diastereoisomers \((R,M)\text{-}7\) (major product) and \((R,P)\text{-}7\) (minor product) were obtained in 54\% yield in a 81.5:18.5 ratio \((\text{\textsuperscript{1}H}\text{NMR})\). Apparently the more rigid binaphthol-based chiral diester bridge of the tetrachloride derived from \((3)\text{-}5\) enforces a more favorable geometry to the two thioxanthene moieties and suppresses oligomer formation through intermolecular coupling. The diastereoisomers \((R,M)\text{-}7\) and \((R,P)\text{-}7\) were readily separated by column chromatography.

It should be emphasized that both a folded and twisted helical shaped structural moiety is present in the same molecule. The two diastereoisomers differ significantly in structure as is visualized in Scheme 2. Although the binaphthyl part is twisted and the thioxanthylidene is folded in both isomers, the formation of the “cross-coupled” product \((R,M)\text{-}7\) is strongly favored over the “linearly coupled” product \((R,P)\text{-}7\). Figure 2 shows an optimized space filling model\textsuperscript{[11]} of \((R,M)\text{-}7\) revealing a double-helix-type structure that is

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme1}
\caption{Synthesis route towards optically active overcrowded alkenes \(\delta\) with \((S,S)\text{-}1\) used as a chiral template. \textit{S} denotes the configuration of the threitol moiety whereas \textit{M} (left-handed helix) and \textit{P} (right-handed helix) define the helicity at the diester side of the overcrowded alkene part of the molecule.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structure}
\caption{ORTEP plot of \((S,S,P)\text{-}5\) (minor product).}
\end{figure}
Scheme 2. Synthetic route towards optically active overcrowded alkenes 7 with \((R)\)-2 used as a chiral template. \(R\) and 5 denote the configuration of the binaphthol moiety whereas \(M\) (left-handed helix) and \(P\) (right-handed helix) define the helicity at the diester side of the overcrowded alkene part of the molecule.

Scheme 3. Cleavage of the chiral bridge (CB) from overcrowded alkenes 5 and 7. \(M\) (left-handed helix) and \(P\) (right-handed helix) define the helicity at the hydroxymethyl-side of 8.

Table 1. Stereochemical correlation and optical rotation data of 5, 7, and 8.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>([\alpha]D^20)^{[a]}</th>
<th>Product</th>
<th>([\alpha]D^20)^{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>((S,S,P))-5 (minor)</td>
<td>+203(^{[a]})</td>
<td>((P))-cis(-8)</td>
<td>-92</td>
</tr>
<tr>
<td>((R,M))-7 (major)</td>
<td>-101</td>
<td>((M))-cis(-8)</td>
<td>+91</td>
</tr>
<tr>
<td>((R,P))-7 (minor)</td>
<td>+120</td>
<td>((P))-cis(-8)</td>
<td>-93</td>
</tr>
<tr>
<td>((S,P))-7 (major)</td>
<td>+100</td>
<td>((P))-cis(-8)</td>
<td>-92</td>
</tr>
<tr>
<td>((S,M))-7 (minor)</td>
<td>-120</td>
<td>((M))-cis(-8)</td>
<td>+91</td>
</tr>
</tbody>
</table>

\([a]\) \(c=1.00,\) CHCl\(_3\), \([b]\) \(c=0.50,\) CHCl\(_3\),

A racemization barrier \((\Delta^*G^\circ)\) of 26.7 ± 0.5 kcal mol\(^{-1}\) (polarimetry) was determined for cis-8, which is in accordance with the observation that the enantiomers of cis-8 are stable at room temperature. A pair of identical CD spectra (except for the sign) were obtained for enantiomers \((P)\)-cis-8 and \((M)\)-cis-8.

Seven maxima were observed for \((M)\)-cis-8 \((n\text{-hexane}/2\text{-propanol} 80/20)\) at wavelengths greater than 220 nm: \(\lambda_{\text{max}}\) \(\Delta\) 230 nm \(-3.5\), 238 \((+17.3)\), 252 \((-6.2)\), 269 \((+25.3)\), 291 \((-38.6)\), 313 \((+18.4)\), 342 \((-10.7)\).

The CD absorptions as well as the \(\Delta\) values are in good agreement with those obtained for related optically pure overcrowded alkenes that were obtained previously by preparative chiral HPLC.

In conclusion, an asymmetric synthesis method, which includes the transfer of axial single bond chirality to axial double bond chirality, for stable optically active overcrowded alkenes has been developed. The determination of the absolute configuration of the major stereoisomer revealed an appealing double-helical structure.

Experimental Section

\((R,M)\)-7 and \((R,P)\)-7 (the same procedure was used for \((S,P)\)-7 and \((S,M)\)-7): Dister \((R)\)-6 (0.73 mmol) was refluxed overnight in oxalyl chloride (20 mL) under a nitrogen atmosphere. The excess of oxalyl chloride was evaporated under reduced pressure. The residue was dissolved in freshly distilled \(p\)-xylene (100 mL) and then activated Cu-bronze (15.90 mmol) was added. This mixture was refluxed overnight. After cooling, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH\(_2\)Cl\(_2\)/n-hexane 3/1) gave \((R,M)\)-7 \((44\% \text{ yield})\) and \((R,P)\)-7 \((10\% \text{ yield})\) as yellow solids. \(\Delta\) \(H\) \(NMR\) (300 MHz, CDCl\(_3\), 25 °C): \(\delta=8.02\) (d, \(3\)H(H)) = 9.15 Hz, 2H; CH), 7.96 (d, \(3\)H(H) = 8.42 Hz, 2H; CH), 7.49 – 7.29 (m, 12H; CH), 7.18 (d, \(3\)H(H) = 8.42 Hz, 2H; CH), 7.07 (m, 2H; CH), 6.77 (m, 2H; CH), 6.42 (d, 2H; CH)).
The racemization barrier (8.42 Hz, 2 H; CH), 6.42 (d, 3 H; CH), 7.13 (d, 3 H; CH), 7.59 – 7.42 (m, 12 H; CH), 7.30 (m, 12 H; CH), 5.00 (d, 2 H; CH). The final refinement on 2909 reflections with F > 2σ(F) was determined by polarimetry (a: 7.22 × 10^7 at 70.0°C).

X-ray crystal structure analysis of (RM)7: Crystal dimensions 0.15 × 0.25 × 0.52 mm, monoclinic, space group P21/m, a = 9.589 Å, b = 14.288 Å, c = 13.01 Å, β = 110.77°, V = 1597.6(8) Å^3. All new compound were fully characterized. The ee value of cis-8 was determined by chiral HPLC (Daicel, Chiralcel OD column, flow rate 1.0 mL/min, n-hexane/isopropanol 99/1; tR 98.1 min for (M)-cis-8 and tR 125.1 min for (P)-cis-8.

The racemization barrier (A*G° of cis-8 was determined by polarimetry (1,2-dibromoethane, k = 7.22 × 10^7 at 70.0°C).

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Keywords: alkenes · asymmetric synthesis · biaryl · chirality · helical structures


[8] Compound 3 was prepared from 4-methoxybenzene and 4-bromophenol in a two-step procedure.


[10] The chirality of this type of helical-shaped distorted alkenes is described by the helicity rule, with P (plus) for a right-handed helix and M (minus) for a left-handed helix, see for example, R. S. Cahn, C. K. Ingold, V. Prelog, Angew. Chem. Int. Ed. Engl. 1966, 5, 385.

[11] The model of (RM)7 was constructed by using Quanta97/CHARMM, which is a product of Molecular Simulations Inc., San Diego, USA. Internet: http://www.msi.com. Dr. Franck Schoonbeek is acknowledged for his assistance.


Influence of Perfluoroarene – Arene Interactions on the Phase Behavior of Liquid Crystalline and Polymeric Materials**

Marcus Weck, Alex R. Dunn, Kozo Matsumoto, Geoffrey W. Coates, Emil B. Lobkovsky, and Robert H. Grubbs*

Supramolecular chemistry, the chemistry of noncovalent intermolecular interactions such as hydrogen bonds, ionic interactions, metal – ion interactions, or the hydrophobic effect, is essential for processes in biological and synthetic systems, such as molecular recognition, catalysis, transport, [4] Prof. R. H. Grubbs, Dr. M. Weck, A. R. Dunn, Dr. K. Matsumoto Arnold and Mabel Beckman Laboratories of Chemical Synthesis Division of Chemistry and Chemical Engineering California Institute of Technology Pasadena, CA 91125 (USA) Fax: (+1)626-564-9297 E-mail: rhg@cco.caltech.edu

Prof. G. W. Coates, Dr. E. B. Lobkovsky Baker Laboratory Deptment of Chemistry & Chemical Engineering Cornell University Ithaca, NY 14853-1301 (USA) Fax: (+1)607-255-4137 E-mail: gc39@cornell.edu

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